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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,004	LI ET AL.	
	Examiner	Art Unit	
	Timothy P. Thomas	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,10 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,10 and 19* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The amendments to the claims, filed 10/16/2006, are acknowledged. Claims 4, 6-9, 11-18 and 20-30 are cancelled. Claims 1-3, 5, 10 and 19 are pending.

2. The 35 USC 112 rejection of claim 19 in the 7/10/2006 office action is withdrawn due to the amendment to the claim. The rejections under 35 USC 102 are still maintained for COPD, with the modifications described below. The double patenting rejections are still maintained.

Claim Objections

3. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1 states that "said disease...is unaccompanied by lung fibrosis"; claim 5, which depends on claim 1 states, "said disease...is at a stage when lung fibrosis is not a **major** symptom". The word "unaccompanied" indicates that **no** lung fibrosis is present, can be detected, etc.; however the presence of "not a major symptom" implies that a minor amount of lung fibrosis may be present. Claim 5 does not introduce any other limitation(s) on claim 1, and therefore, does not further limit claim 1 in its current form.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2, 10 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Some of the species of diseases/conditions listed in claim 2 normally involve a measure of lung fibrosis; for instance, cystic fibrosis is a type of lung fibrosis. This is inconsistent with the requirement of claim 1 that "said disease...is unaccompanied by lung fibrosis".

Claim 10 depends on claim 9, which has been cancelled. It is not clear that the metes and bounds of the "small organic molecules" claimed still exclude peptides. Claim 19 depends on claim 10, and is therefore also indefinite.

The term "small", in claims 10 and 19, is a relative term and does not render the claim definite. There are some chemists, for instance, those who work with single amino acids, that would not consider some disclosed compounds, such as LXVL, to be "small" organic molecules, whereas others that study proteins and polymers probably would.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 5 and 10 are rejected under 35 U.S.C. 102(a & e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cuenoud et al. (US 2004/0038951 A1).

Cuenoud teaches a method of treating an inflammatory or obstructive airways disease by administration of a medicament including a corticosteroid to a subject in need of such treatment, specifically taught are patients that include those less than 4 or 5 years of age, diagnosed as "wheezy infants", "an established patient category of major medical concern" (abstract; paragraph 0004; paragraph 0038); which exhibit bronchodilatory and anti-inflammatory properties (improvement of lung function; paragraph 0037). Diseases and conditions to which the invention is applicable include emphysemia, chronic bronchitis, COPD, ARDS, asthma, acute lung injury, and pneumoconiosis, such as asbestosis and tobacosis (lung injuries resulting from inhaled toxins (paragraphs 0038, 0040). An inherent property of the administration of corticosteroids (small organic molecules) to patients that have lung conditions, such as asthma, is inhibition of expression of TGF-beta1 (a biological activity that is mediated by

a TGFbeta-R1 kinase receptor is the inflammation associated with the expression of TGF-beta1), which is taught by Miller, et al (2006; Am. J. Physiol. Lung Cell. Mol. Physiol. 290:L162-L169; abstract). The conditions taught by Ceunoud listed here are also those listed in the instant claim 2, that fall into the category of "unaccompanied by lung fibrosis", required by the independent claim 1; therefore, lung fibrosis would not be "a major symptom" of these conditions, as required by claim 5.

In the alternative, it might be argued that the method taught by Cuenoud does not involve the step of administration to "a mammalian subject diagnosed with" the diseases and conditions taught, other than for "wheezy infants", a subgroup of patients with asthma. Cuenoud does not specifically teach administration to a "mammalian" subject, although the phrases "wheezy infants", "an established patient category of major medical concern", and the specified age range imply this. Cuenoud also does not specifically mention diagnosed patient groups, except for the wheezy infants. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the medicament to mammalian; specifically to human patients, who have been diagnosed with one of the conditions or diseases taught by Cuenoud. The motivation to administer to mammals or humans would be to help the human patients that suffer with these conditions or to study the feasibility in mammals for treatment of the conditions with the goal of developing effective medical therapies for human patients. The motivation to administer the medicament to patients who have been diagnosed with the conditions would be one of cost consideration; the administration of a drug is more effective when administered to a patient population for which efficacy

has been established, and therefore would be more cost effective than administration to patients before diagnosis.

8. Claims 1, 2, 5, 10, and 19 are rejected under 35 U.S.C. 102(a & e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Axon (WO 2004/024159 A1).

Axon teaches TGFβ inhibitors with the instant structural formula 2 of claim 19, which are "useful in treating diseases mediated by the activity of this family of factors" (formula 1, paragraph 0008), including prophylactic or therapeutic treatment of mammals and humans with conditions characterized by excessive activity of TGFβ (paragraph 0044); and as previously described, treatment of specific conditions associated with lung fibrosis, including COPD (paragraph 0004). Axon teaches all of the currently claimed substituents for instant formula 2: Ar preferred substituents taught are optionally substituted phenyl, 2-, 3- or 4-pyridyl, indolyl, 2- or 4-pyrimidyl, pyridazinyl, benzotriazol or benzimidazolyl (paragraph 0025); NR^1 and S are taught for X (p. 3, 3rd indentation); R^1 is H, alkyl (1-8C), alkenyl (2-8C), or alkynyl (2-8C) (p.3, 4th indentation); all of the R^3 and R^4 substituents are taught (p. 3, 11th and 12th indentations); as are R^2 substituents (p. 3 last paragraph); n is 0-5 (p. 3, 5th indentation). **Prophylactic** treatment of a human patient with COPD would be at a stage where the condition would be unaccompanied by lung fibrosis and when lung fibrosis is not a major symptom. Identification of a human with the condition of COPD would inherently involve diagnosis of that patient.

In the alternative view, it might be viewed that Axon does not specifically teach administration to a subject that has been "diagnosed" with COPD. It would have been obvious to one skilled in the art to treat a patient that has been diagnosed with a condition; the medical profession is taught to diagnose patients so that drug therapy is more effective. The motivation to do so is cost savings; it is more cost-effective to treat a patient that has first been diagnosed with a condition for which a drug is known to be effective.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-3, 5, 10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Axon, et al (WO 2004/024159 A1) in view of any one of the following: Marwick, et al. (2002 Nov; Ann. N Y Acad. Sci.; 973:278-83); Dhainaut, et al (2003 Apr; Crit. Care Med.; 31 (4 Suppl):S258-64); Vignola, et al. (1997; Monaldi Arch. Chest Dis.; 52(2):159-69); Song, et al. (2001 May; Zhonghua Jie He He Hu Xi Za Zhi. (Chinese journal of tuberculosis and respiratory diseases); 24(5):283-7; English abstract; PubMed ID: 11802977); Arkwright, et al (2000; Thorax; 55(6):459-62); or Fahy, et al. (2003 Apr; Am. J. Respir. Cell Mol. Biol.; 28(4):499-503).

Axon teaches TGFβ inhibitors with the instant structural formula 2 of claim 19, as described above. With the exception of COPD (which is taught), Axon does not specifically teach any of the other species of diseases listed in the instant claims 2-3. Each of the second group of references teaches an association of TGFβ activity to one or more of these species of diseases, indicating or implying that inhibition of TGFβ is likely to be an effective therapy for treatment of the disease(s). Marwick teaches cigarette smoke-induced oxidative stress (lung injury resulting from inhaled toxins), emphysema, and COPD are associated with a chronic inflammatory response, and is

associated with increased expression of TGFβ1 (title; abstract; p. 279, 3rd paragraph). Dhainaut teaches levels of TGFβ are increased as early as 2 days after the induction of injury in acute respiratory distress syndrome and acute lung injury; inhibition of TGFβ protected mice from pulmonary edema induced by bleomycin or Escherichia coli endotoxin (lung injuries from infections causes and circulating or inhaled toxins) and protected patients during ARDS; indicating that TGFβ may be active early in acute lung injury and blocking TGFβ may be an effective treatment (title; abstract). Vignola teaches asthma as a chronic inflammatory disease and possible correlation to TGFβ in asthma and chronic bronchitis. Song teaches COPC established by intratracheal instillation of lipopolysaccharide (lung injuries from circulating exogenous toxins) and exposure to cigarette smoke correlated to increased expressions of TGFβ1 and that intervention against TGFβ1 may be of use in the inhibition of airway remodeling in COPD (abstract). Arkwright teaches patients with cystic fibrosis with high TGFβ1 production had more rapid deterioration in lung function than those with lower TGFβ1 production (abstract). Fahy teaches activation of TGFβ1 may be important in the early phases of acute lung injury and may lead to new therapies for ARDS by targeting inhibition of fibrosis (abstract).

In view of the suggestions from the second group of references it would have been obvious to one skilled in the art at the time of the invention to administer the compounds taught by Axon to mammalian patients with any of the conditions taught by the second group of references or for any other related lung condition where inflammation plays a role (i.e., all of the disease species of the instant claims 2-3), since

TGFβ is associated with inflammation. The motivation to do so is to extend potential effective drug therapies to patients with these diseases. It would also have been obvious to treat patients that have been diagnosed with one of the conditions; the motivation would be cost effectiveness.

Double Patenting

13. The double patenting rejection of claims 1-2, 5, 10 and 19 with copending Application No. 10/660115, described in the 7/10/2006 office action, is maintained.

Conclusion

14. Pending claims 1-3, 5, 10 and 19 are rejected. Claim 5 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy P. Thomas whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TPT/
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